09/841025

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> d his

     (FILE 'HOME' ENTERED AT 14:36:00 ON 10 APR 2002)

     FILE 'REGISTRY' ENTERED AT 14:36:07 ON 10 APR 2002
                E 99294-93-6/RN
L1             1 S E3

     FILE 'CAPLUS' ENTERED AT 14:37:38 ON 10 APR 2002
L2            25 S L1
L3             1 S L2 AND HYDRATE
L4            24 S L2 NOT L3
L5             1 S L4 AND POLYMORPH?
L6            23 S L4 NOT L5

     FILE 'STNGUIDE' ENTERED AT 14:43:11 ON 10 APR 2002

     FILE 'CAPLUS' ENTERED AT 14:49:26 ON 10 APR 2002
L7             2 S ZOLPIDEM (P) HYDRATE?
L8             0 S L7 NOT L2
L9             3 S ZOLPIDEM (P) POLYMORPH?
L10            2 S L9 NOT L2

     FILE 'STNGUIDE' ENTERED AT 14:52:40 ON 10 APR 2002

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09/841025

L10 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS
AN 1999:310588 CAPLUS
DN 131:96890
TI Pharmacologic and behavioral responses of inbred C57BL/6J and Strain 129/SvJ mouse lines
AU Homanics, Gregg E.; Quinlan, Joseph J.; Firestone, Leonard L.
CS Departments of Anestheshiology/Critical Care Medicine and Pharmacology, University of Pittsburgh, Pittsburgh, PA, 15261, USA
SO Pharmacol., Biochem. Behav. (1999), 63(1), 21-26
CODEN: PBBHAU; ISSN: 0091-3057
PB Elsevier Science Inc.
DT Journal
LA English
AB Gene-targeting technol. is creating an explosion in the no. of animals available with single gene mutations that affect the function of the central nervous system. Most gene-targeted mice are produced on a mixed genetic background of C57BL/6J and substrains of Strain 129. Understanding the behavioral characteristics and responses to various drugs of these parental strains is vital to interpreting data from gene-targeted mice. We directly compared C57BL/6J and Strain 129/SvJ mouse lines on several behavioral paradigms and in response to several hypnotic and anesthetic drugs. Compared to Strain 129/SvJ mice, C57BL/6J animals are more sensitive to the hypnotic effects of midazolam, **zolpidem**, and propofol, less sensitive to etomidate and ethanol, and do not differ in sensitivity to Ro15-4513 or pentobarbital. These strains do not differ in their sensitivity to the motor ataxic effects of the volatile anesthetics enflurane or halothane. However, Strain 129/SvJs are more sensitive to the immobilizing effects of halothane but not enflurane. Motor coordination differs initially, but with repeated testing strain differences are no longer apparent. Strain 129/SvJ mice are more anxious on the elevated plus maze and open-field activity assays. Thus, these mouse strains harbor **polymorphisms** that influence some, but not all, traits of interest to behavioral neuroscientists.
RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS
AN 1996:726605 CAPLUS
DN 126:54294
TI The use of adult human hepatocytes in primary culture and other in vitro systems to investigate drug metabolism in man
AU Maurel, Patrick
CS INSERM U-128, CNRS, BP5051, 1919 Route de Mende, 34033, Montpellier, Fr.
SO Adv. Drug Delivery Rev. (1996), 22(1,2), 105-132
CODEN: ADDREP; ISSN: 0169-409X
PB Elsevier
DT Journal; General Review
LA English
AB A review with 140 refs. Among the numerous enzyme systems involved in the metab. of xenobiotics, cytochromes P 450 (CYP) from families CYP1, 2 and 3 play a prominent role. These cytochromes are monoxygenases mainly expressed in the liver. They are able to oxidize an apparently unlimited no. of compds. and, on some occasions, generate cytotoxic or genotoxic metabolites responsible for various pathologies including hepatitis and chem. carcinogenesis. The expression and function of these cytochromes might be affected by a no. of factors including, physiol. (hormones, growth factors, cytokines, etc.), pathol. (infections, inflammation, hepatectomy, etc.), genetic (**polymorphism** of expression or function) and environmental (drugs, diet compds., pollutants) factors. These various properties account for the wide interindividual variability exhibited by the human populations in response to drugs and environmental pollutants in terms of metab. and toxicity. From the anal. of a no. of clin. reports focusing on adverse drug effects and from the above considerations, it appears that answering the following questions is absolutely required before a new drug is administered to man with max. safety: (1) What is the metabolic pathway of the drug and what are the main metabolites (2) Which enzyme system is involved in the metab. of the drug (3) Is the drug an inducer or inhibitor of drug metabolizing enzymes (4) What are the possible drug interactions (5) Can the drug be activated to cytotoxic or genotoxic metabolites In this chapter, I shall describe the various human hepatocyte culture systems used in this and other labs., and show how the use of these cultures, in combination with the other in vitro systems including human liver microsomes, may help to answer the above questions concerning several drugs including: diazepam, ketotifen, **zolpidem**, omeprazole, lansoprazole, cyclosporin A, clometacin and cyproterone acetate. Emphasis will be placed on the comparison between the results obtained in vitro and the situation in man in vivo, as well as on the prediction, confirmation and/or a posteriori explanation of clin.

observations.

L3 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
AN 2001:780683 CAPLUS
DN 135:335156
TI Modified-release formulations containing a hypnotic agent
IN Platteeuw, Johannes Jan; Van Den Heuvel, Dennie Johan Marijn; Van Dalen, Frans; Lemmens, Jacques Maria
PA Synthon B.V., Neth.
SO PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001078725	A2	20011025	WO 2001-NL299	20010412
WO 2001078725	A3	20011220		

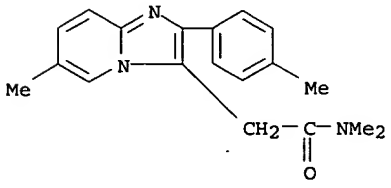
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
US 2000-196939PP 20000413

AB Hypnotic pharmaceutical compns. are made from pellets and exhibit a modified release. Zolpidem or a pharmaceutically acceptable salt thereof is a typical hypnotic. The pellets are preferably spherical and exhibit a dissoln. profile that includes 60% of the hypnotic agent being released from the pellet not earlier than 5 min from the start of a specified in vitro dissoln. test. Although the modified release profile can include 50 of the hypnotic agent being released not earlier than 15 min after the start of the dissoln. test, the pellet preferably does not contain a release rate controlling excipient or coating. Instead, microcryst. cellulose and the active constitute the majority of the pellet, e.g. 90 or more. Spherical pellets are also made by a convenient method that is applicable to any pharmaceutically active agent. Microcryst. cellulose 1703, zolpidem hydrochloride **hydrate** 189.2 g, and water 1892 mL were mixed and stirred for 15 min. Water was then removed and the resulted pellets were dried and fractionated by sieving.

IT **99294-93-6**, Zolpidem tartrate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(modified-release formulations contg. hypnotic agent)
RN 99294-93-6 CAPLUS
CN Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

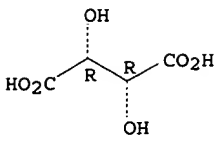
CRN 82626-48-0
CMF C19 H21 N3 O



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.



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     FILE 'REGISTRY' ENTERED AT 14:36:07 ON 10 APR 2002
                E 99294-93-6/RN
L1             1 S E3

     FILE 'CAPLUS' ENTERED AT 14:37:38 ON 10 APR 2002
L2            25 S L1
L3             1 S L2 AND HYDRATE

=> s l2 not l3
L4            24 L2 NOT L3

=> s l4 and polymorph?
          118767 POLYMORPH?
L5             1 L4 AND POLYMORPH?

=> d fbib abs hitstr

L5   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2002 ACS
AN   2001:798053  CAPLUS
DN   135:348889
TI   Zolpidem hemitartrate polymorphs for treatment of insomnia
IN   Aronhime, Judith; Dolitzky, Ben-Zion; Kordova, Marco; Leonov, David;
     Meszaros-Sos, Erzebet; Salyi, Szaboles; Schwartz, Anchel; Szabo, Csaba;
     Zavurov, Shlomo
PA   Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA,
     Inc.
SO   PCT Int. Appl., 58 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
PI   WO 2001080857     A1    20011101       WO 2001-US13175  20010424
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
             HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
             LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,
             RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,
             VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
                                            US 2000-199298PP 20000424
                                            US 2000-206025PP 20000522
                                            US 2000-225364PP 20000814
AB   The present invention provides for novel polymorphs of zolpidem
     hemitartrate and the prepn. of the polymorphs. The zolpidem
     hemitartrate are prepd. as hydrates or solvates, e.g., zolpidem
     hemitartrate methanolate or acetonate. For example, 5 g (17.7 mmol) of
     zolpidic acid was suspended in 50 mL of toluene and 0.15 mL of DMF and the
     mixt. was cooled to 15-28.degree.. Then, 1.7 mL (23.3 mmol) of thionyl
     chloride was added into the mixt. at this temp. for 1 h, then it is
     stirred for 4 h at 35-40.degree.. After formation of acid chloride the
     thionyl chloride excess was removed by distn. The vol. of the reaction
     mixt. was adjusted to 50 mL by toluene, then it was cooled to
     -5-0.degree., and dimethylamine gas was introduced into the reaction mixt.
     until the pH was 8.5-9.5. Pptn. of zolpidem base started almost
     immediately. The suspension was cooled to -10-(-12).degree. and mixed for
     1 h. The crude product was filtered and washed consecutively with
     toluene, 5% cooled water soln. of NH4CO3 and cooled water. The product
     was dried under vacuum to obtain 4.1 g (yield 80%) zolpidem base used in
     prepn. of hemitartrate polymorphs.
IT   99294-93-6P, Zolpidem hemitartrate
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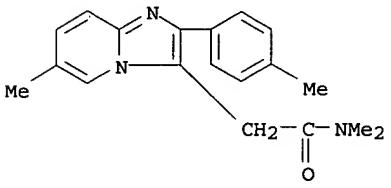
this appl.

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and characterization of zolpidem hemitartrate **polymorphs** for insomnia treatment)

RN 99294-93-6 CAPLUS
CN Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

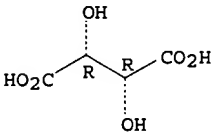
CRN 82626-48-0
CMF C19 H21 N3 O



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.



RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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(FILE 'HOME' ENTERED AT 14:36:00 ON 10 APR 2002)

FILE 'REGISTRY' ENTERED AT 14:36:07 ON 10 APR 2002
E 99294-93-6/RN
L1 1 S E3

FILE 'CAPLUS' ENTERED AT 14:37:38 ON 10 APR 2002
L2 25 S L1
L3 1 S L2 AND HYDRATE
L4 24 S L2 NOT L3
L5 1 S L4 AND POLYMORPH?

=> s l4 not l5
L6 23 L4 NOT L5

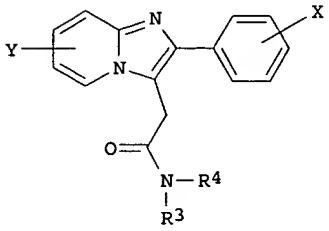
=> d 1-23 fbib abs hitstr

L6 ANSWER 1 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 2002:47557 CAPLUS
DN 136:102382
TI A process for the preparation of 2-phenyl-imidazo[1,2-a]pyridine-3-acetamides
IN Castaldi, Graziano
PA Dinamite Dipharma S.P.A. (In Abbreviated Form Dipharma S.P.A.), Italy
SO Eur. Pat. Appl., 18 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

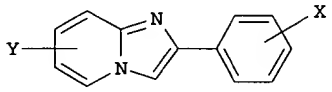
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 1172364	A1	20020116	EP 2001-116016	20010702
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
				IT 2000-MI1591 A	20000714
	US 2002019528	A1	20020214	US 2001-902616	20010712
				IT 2000-MI1591 A	20000714

OS CASREACT 136:102382; MARPAT 136:102382

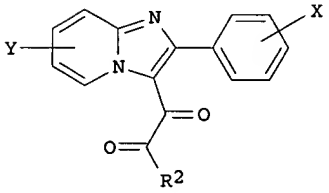
GI



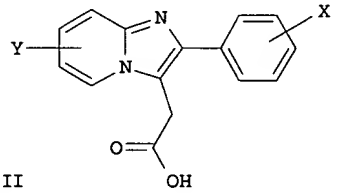
I



II



III



IV

AB A process for the prepn. of 2-phenyl-imidazo[1,2-a]pyridine-3-acetamides (I; X = H, halo, C1-4 alkyl, C1-6 alkoxy, CF3, MeS, NO2, MeSO2; Y = H, halo, C1-4 alkyl; R3, R4 = H, C1-5 alkyl, allyl, propargyl, C3-6 cycloalkyl, CH2Ph, Ph) comprises the reaction of a 2-phenyl-imidazo[1,2-a]pyridine (II; X, Y = same as above) with an oxalic ester reactive deriv. of formula R1COCOR2 (R1 = halo, a carboxy-activating group; R2 = C1-6 alkoxy or phenoxy both optionally substituted with C1-6 alkyl or alkoxy, C1-6 alkylamino, arylamino), followed by reducing the carbonyl group of the resulting glyoxalate esters (III; R2 = = same as above) and reacting the resulting carboxylic acids (IV; X, Y = same as above) with an amine of formula NHR3R4. This process provides an efficient, convenient route for the prepn. of 2-phenylimidazo[1,2-a]pyridine-3-acetamides, in particular zolpidem. All known synthesis of zolpidem used either reagents com. available with difficulty, toxic reagents, or industrially unsuitable procedures due to low yields and/or products with poor purity which should undergo repeated purifn. procedures. Under the best operative conditions, this method gives zolpidem of suitable quality and in yields above 80%, starting from imidazopyridine. Thus, chlorination of potassium monoethyl oxalate with POCl3 in CH2Cl2 at .apprx.30.degree. for 4-6 h followed by acylation of 2-(4-methylphenyl)-6-methylimidazo[1,2-a]pyridine with the resulting oxalic acid chloride Et ester in the presence of Et3N under reflux for 1 h gave 97.5% Et 2-(4-methylphenyl)-6-methylimidazo[1,2-a]pyridine-3-glyoxalate (V). Sapon. of V with NaOH in aq. EtOH under reflux, followed by condensation with hydrazine under reflux for 14 h and distn. in the presence of KOH at 122-14.degree. under refluxing until N evolution ceased gave, after acidification with AcOH, 96.5% 2-(4-methylphenyl)-6-methylimidazo[1,2-a]pyridine-3-acetic acid (VI). Chlorination of VI with oxalyl chloride in CH2Cl2 under reflux for 30 min and amidation with dimethylamine hydrochloride at room temp. for 1 h gave zolpidem which was converted into zolpidem oxalate.

IT **99294-93-6P**, Zolpidem tartrate
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for prepn. of 2-phenylimidazo[1,2-a]pyridine-3-acetamides)

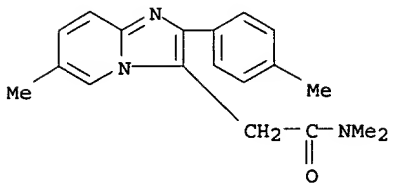
RN 99294-93-6 CAPLUS

CN Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

09/841025

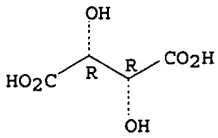
CRN 82626-48-0
CMF C19 H21 N3 O



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.

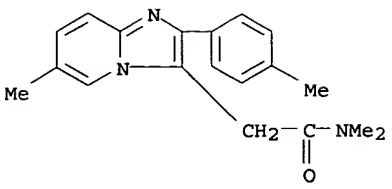


RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 2001:534729 CAPLUS
DN 135:352280
TI High-performance liquid chromatographic determination of zolpidem tartrate in human plasma with fluorometric detection
AU Song, Hongjie; Li, Zhen; Shi, Jing; Fan, Guorong; Jin, Guilan; Hu, Jinhong
CS Department of Clinical Pharmacology, Shanghai Changhai Hospital, Shanghai, 200433, Peop. Rep. China
SO Zhongguo Yaoxue Zazhi (Beijing, China) (2001), 36(5), 333-335
CODEN: ZYZAEU; ISSN: 1001-2494
PB Zhongguo Yaoxue Zazhishe
DT Journal
LA Chinese
AB The level of zolpidem tartrate in human plasma was detd. by HPLC at excitation wavelength of 254 nm and emission wavelength of 390 nm on Hypersil ODS2 column with MeCN-0.02M KH2PO4 buffer (pH 6.0) (40:60) as mobile phase and flow rate of 1.0 mL min-1. The plasma sample was treated with 0.25M KOH soln. and extd. with Et2O. The linear range was 5.0-250 ng mL-1 (r = 0.999 5, n = 6). The detection limit was 2.5 ng mL-1. The mean recoveries of high, medium, and low concns. were (103.60 .+-. 2.44), (104.40 .+-. 0.84), and (106.64 .+-. 9.93)%, resp. The results showed that the method may be a reliable quant. method for pharmacokinetic study of zolpidem.
IT **99294-93-6**, Zolpidem tartrate
RL: ANT (Analyte); ANST (Analytical study)
(high-performance liq. chromatog. detn. of zolpidem tartrate in human plasma with fluorometric detection)
RN 99294-93-6 CAPLUS
CN Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

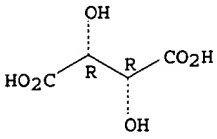
CRN 82626-48-0
CMF C19 H21 N3 O



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.



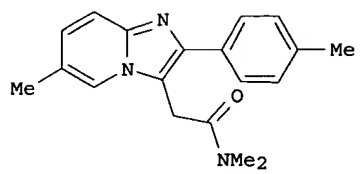
L6 ANSWER 3 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 2001:396866 CAPLUS
DN 135:19639
TI Process for the preparation of 6-methyl-2-(4-methylphenyl)-imidazo[1,2-a]pyridine-3-(N,N-dimethyl)acetamide and intermediates
IN Pongo, Laszlo; Reiter, Jozsef; Simig, Gyula; Toempe, Peter; Hoffmanne Fekete, Valeria; Rivo, Endre; Koncz, Laszlo; Vereczkeyne Donath, Gyoergyi; Nagy, Kalman
PA Egis Gyogyszergyar Rt., Hung.
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001038327	A2	20010531	WO 2000-HU120	20001122

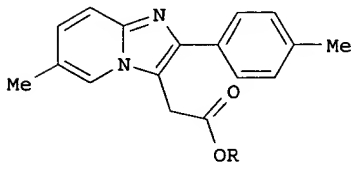
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

HU 1999-4377 A 19991122
HU 1999-4379 A 19991122

OS CASREACT 135:19639; MARPAT 135:19639
GI



I



II

AB The invention relates to a new and improved process for the prepn. of the title compd. I and its pharmaceutically acceptable acid addn. salts which comprises reacting an ester II (wherein R = alkyl, phenylalkyl) in a polar protic or aprotic solvent with Me2NH and, if desired, converting the compd. I thus obtained into a pharmaceutically acceptable acid addn. salt. The compd. I is a known valuable sedative used in therapy and marketed under the INN Zolpidem (no data).

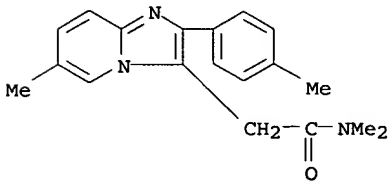
IT **99294-93-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for the prepn. of 6-methyl-2-(4-methylphenyl)-imidazo[1,2-a]pyridine-3-(N,N-dimethyl)acetamide and intermediates)

RN 99294-93-6 CAPLUS

CN Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

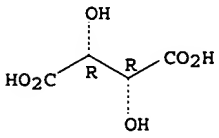
CRN 82626-48-0
CMF C19 H21 N3 O



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.



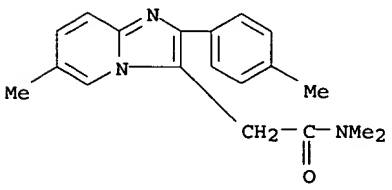
L6 ANSWER 4 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 2001:283457 CAPLUS
DN 135:205414
TI Zolpidem and triazolam interact differentially with a delay interval on a digit-enter-and-recall task

09/841025

AU Rush, Craig R.; Baker, Robert W.
CS Department of Behavioral Science, University of Kentucky, Lexington, KY, 40536-0086, USA
SO Human Psychopharmacology (2001), 16(2), 147-157
CODEN: HUPSEC; ISSN: 0885-6222
PB John Wiley & Sons Ltd.
DT Journal
LA English
AB Zolpidem (AMBIEN), an imidazopyridine, is now the most commonly prescribed hypnotic in the United States. Zolpidem is neuropharmacol. distinct from benzodiazepine hypnotics in that it binds with low affinity to .alpha.5-contg. GABAA-receptor subtypes. Despite its unique benzodiazepine-receptor binding profile, the results of most of the published studies conducted with humans suggest that the abs. magnitude of impairment produced by zolpidem is comparable to that obsd. with benzodiazepine hypnotics like triazolam. The present study compared the acute effects of zolpidem (0, 7.5, 15 and 22.5 mg) and triazolam (0, 0.1875, 0.375 and 0.5625 mg) in 10 non-drug-abusing humans using a Digit-Enter-and-Recall task with varying delay intervals (0, 10 and 20 s). To more fully characterize the behavioral effects of zolpidem and triazolam, several other performance tasks and subject-rated drug-effect questionnaires were included. Zolpidem and triazolam impaired performance on the Digit-Enter-and-Recall task as a function of dose under all delay intervals. However, the dose-related effects of the drugs interacted differentially with the delay interval such that zolpidem produced significantly less impairment than triazolam following the longest delay (i.e., 20 s). Zolpidem and triazolam produced comparable dose-related impairment on the digit symbol substitution test (DSST), circular lights task, and picture recall/recognition task. Zolpidem and triazolam generally produced qual. and quant. similar subject-rated drug effects, although some between-drug differences were obsd. Consistent with the pharmacokinetics of these drugs, the effects of zolpidem peaked sooner and were shorter in duration than those obsd. with triazolam. The results of this expt. suggest that zolpidem may have less potential than triazolam to impair recall, which may be due to differences between these compds. in terms of their benzodiazepine-receptor binding profile. The results of the present study are also concordant with previous studies that found that drugs that act at the GABAA-receptor complex can be differentiated based on their interaction with the delay interval on a Digit-Enter-and-Recall task.
IT **99294-93-6**, AMBIEN
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(zolpidem and triazolam interact differentially with a delay interval on a digit-enter-and-recall task)
RN 99294-93-6 CAPLUS
CN Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

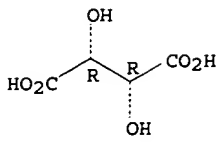
CRN 82626-48-0
CMF C19 H21 N3 O



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.



RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 2001:10601 CAPLUS
DN 134:76391
TI Timed dual release dosage forms comprising a short acting hypnotic or a salt thereof
IN Alaux, Gerard; Andre, Frederic; Ducassou, Jean; Lewis, Gareth
PA Sanofi-Synthelabo, Fr.
SO Eur. Pat. Appl., 17 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP 1064937	A1	20010103	EP 1999-401605	19990628
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
WO 2001000181	A2	20010104	WO 2000-EP6792	20000627
WO 2001000181	A3	20010301		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
			EP 1999-401605 A	19990628
BR 2000011994	A	20020305	BR 2000-11994	20000627
			EP 1999-401605 A	19990628
			WO 2000-EP6792 W	20000627

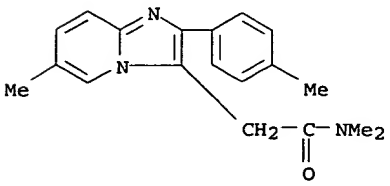
AB The invention relates to timed dual release dosage forms of short acting hypnotics or salts adapted to release the short-acting hypnotic over a predetd. time, according to a profile of dissoln. characterized in that it comprises two release pulses, the first being immediate and the second being delayed by a fixed time. Immediated-release pellets contg. zolpidem hemitartrate were prepd. and coated pellets contg. zolpidem hemitartrate, tartaric acid and benzalkonium chloride prepd. and coated with a Eudragit RS100/RL100 soln.

IT **99294-93-6**, Zolpidem hemitartrate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(timed dual release dosage forms comprising a short acting hypnotic or a salt)

RN 99294-93-6 CAPLUS
CN Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

CRN 82626-48-0
CMF C19 H21 N3 O

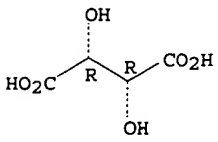


CM 2

09/841025

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.



RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 2000:861473 CAPLUS
DN 134:32972
TI Porous drug matrixes containing polymers and sugars and methods of their manufacture
IN Straub, Julie; Bernstein, Howard; Chickering, Donald E., III; Khatak, Sarwat; Randall, Greg
PA Acusphere, Inc., USA
SO PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000072827	A2	20001207	WO 2000-US14578	20000525
WO 2000072827	A3	20010125		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
			US 1999-136323PP	19990527
			US 1999-158659PP	19991008
			US 1999-433486 A	19991104
			US 2000-186310PP	20000302
EP 1180020	A2	20020220	EP 2000-939365	20000525
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
			US 1999-136323PP	19990527
			US 1999-158659PP	19991008
			US 1999-433486 A	19991104
			US 2000-186310PP	20000302
			WO 2000-US14578W	20000525
NO 2001005753	A	20020128	NO 2001-5753	20011126
			US 1999-136323PP	19990527
			US 1999-158659PP	19991008
			US 1999-433486 A	19991104
			US 2000-186310PP	20000302
			WO 2000-US14578W	20000525

AB Drugs, esp. low aq. soly. drugs, are provided in a porous matrix form, preferably microparticles, which enhances dissoln. of the drug in aq. media. The drug matrixes preferably are made using a process that includes (i) dissolving a drug, preferably a drug having low aq. soly., in a volatile solvent to form a drug soln., (ii) combining at least one pore forming agent with the drug soln. to form an emulsion, suspension, or second solns., and (iii) removing the volatile solvent and pore forming agent from the emulsion, suspension, or second soln. to yield the porous matrix of drug. The pore forming agent can be either a volatile liq. that is immiscible with the drug solvent or a volatile solid compd., preferably a volatile salt. In a preferred embodiment, spray drying is used to remove the solvents and the pore forming agent. The resulting porous matrix has a faster rate of dissoln. following administration to a patient, as compared to non-porous matrix forms of the drug. In a preferred embodiment, microparticles of the porous drug matrix are reconstituted with an aq. medium and administered parenterally, or processed using std. techniques into tablets or capsules for oral

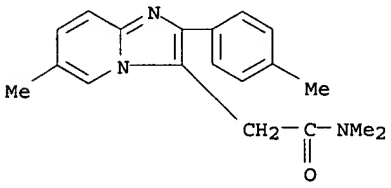
administration. Paclitaxel or docetaxel can be provided in a porous matrix form, which allows the drug to be formulated without solubilizing agents and administered as a bolus. For example, a nifedipine-loaded org. soln. was prepd. by dissolving 9.09 g of PEG 3350, 2.27 g of nifedipine, and 0.009 g of lecithin in 182 mL of methylene chloride. An aq. soln. was prepd. by dissolving 3.27 g of NH4HCO3 and 0.91 g of PEG 3350 in 1.82 mL of water. The aq. and org. solns. were homogenized and resulting emulsion was spray dried. A suspension of the porous nifedipine drug matrix was prepd. in 5% dextrose soln. at a concn. of 2.5 mg/mL. A bolus injection of the suspension was tolerated when administrated to dogs.

IT **99294-93-6**, Zolpidem tartrate
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(prepn. of porous matrixes contg. hydrophilic polymers and sugars for enhancement of drug dissoln.)

RN 99294-93-6 CAPLUS
CN Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

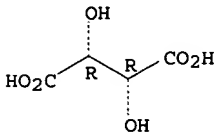
CRN 82626-48-0
CMF C19 H21 N3 O



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.



L6 ANSWER 7 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 2000:707165 CAPLUS
DN 133:281780
TI Preparation of zolpidem salts with improved stability and manufacturability.
IN Ettema, Gerrit Jan Bouke; Lemmens, Jacobus Maria; Peters, Theodorus Hendricus Antonius; Picha, Frantisek
PA Synthon B.V., Neth.
SO PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000058310	A1	20001005	WO 2000-NL171	20000313

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

				US 1999-126494PP	19990325
				EP 1999-203478 A	19991022
				US 1999-449974 A	19991126
EP 1038875		A2	20000927	EP 1999-203478	19991022
EP 1038875		A3	20010912		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
				US 1999-126494PP	19990325
US 6242460		B1	20010605	US 1999-449974	19991126
				US 1999-126494PP	19990325
EP 1163241		A1	20011219	EP 2000-913159	20000313
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
				US 1999-126494PP	19990325
				EP 1999-203478 A	19991022
				US 1999-449974 A	19991126
				WO 2000-NL171 W	20000313

PATENT FAMILY INFORMATION:

FAN 2000:686287

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 1038875	A2	20000927	EP 1999-203478	19991022
	EP 1038875	A3	20010912		
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				US 1999-126494PP	19990325
	US 6281360	B1	20010828	US 2000-512789	20000225
				US 1999-126494PP	19990325
	NL 1014634	C1	20000803	NL 2000-1014634	20000313
				US 1999-126494PP	19990325
				EP 1999-203478 A	19991022
				US 1999-449974 A	19991126
	WO 2000058310	A1	20001005	WO 2000-NL171	20000313
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
				US 1999-126494PP	19990325
				EP 1999-203478 A	19991022
				US 1999-449974 A	19991126
	EP 1163241	A1	20011219	EP 2000-913159	20000313
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
				US 1999-126494PP	19990325
				EP 1999-203478 A	19991022
				US 1999-449974 A	19991126
				WO 2000-NL171 W	20000313

AB A zolpidem salt, excluding the salt zolpidem tartrate, exhibiting a melting endotherm corresponding to zolpidem free base upon heating from about 20.degree. to about 250.degree. at 5.degree./min., is claimed. Thus, zolpidem was added to MeSO3H in acetone followed by 10 min. stirring, heating to 50.degree., and cooling to room temp. to give zolpidem mesylate. This showed a soly. of 432.03 mg/mL H2O, vs. 18.78 mg/mL for zolpidem tartrate.

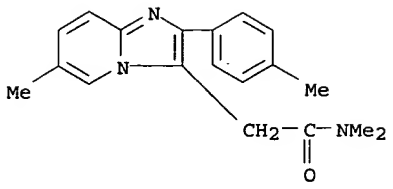
IT **99294-93-6P**, Zolpidem tartrate
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of zolpidem salts with improved stability and manufacturability)

RN 99294-93-6 CAPLUS

CN Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

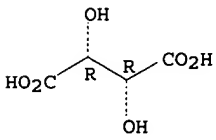
CRN 82626-48-0
CMF C19 H21 N3 O



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 8 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 2000:686287 CAPLUS
DN 133:252434
TI Imidazopyridine derivatives and process for making them
IN Ettema, Gerrit Jan Bouke; Lemmens, Jacobus Maria; Peters, Theodorus Hendricus Antonius; Picha, Frantisek
PA Synthon B.V., Neth.
SO Eur. Pat. Appl., 15 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP 1038875	A2	20000927	EP 1999-203478	19991022
EP 1038875	A3	20010912		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
			US 1999-126494PP	19990325
US 6281360	B1	20010828	US 2000-512789	20000225
			US 1999-126494PP	19990325
NL 1014634	C1	20000803	NL 2000-1014634	20000313
			US 1999-126494PP	19990325
			EP 1999-203478 A	19991022
			US 1999-449974 A	19991126
WO 2000058310	A1	20001005	WO 2000-NL171	20000313
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
			US 1999-126494PP	19990325
			EP 1999-203478 A	19991022
			US 1999-449974 A	19991126
EP 1163241	A1	20011219	EP 2000-913159	20000313
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
			US 1999-126494PP	19990325
			EP 1999-203478 A	19991022
			US 1999-449974 A	19991126
			WO 2000-NL171 W	20000313

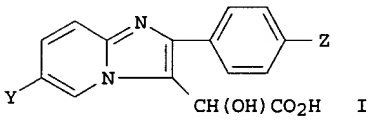
PATENT FAMILY INFORMATION:
FAN 2000:707165

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI	WO 2000058310	A1	20001005	WO 2000-NL171	20000313
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
				US 1999-126494PP	19990325
				EP 1999-203478 A	19991022
				US 1999-449974 A	19991126
	EP 1038875	A2	20000927	EP 1999-203478	19991022
	EP 1038875	A3	20010912		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
				US 1999-126494PP	19990325
	US 6242460	B1	20010605	US 1999-449974	19991126
				US 1999-126494PP	19990325
	EP 1163241	A1	20011219	EP 2000-913159	20000313
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
				US 1999-126494PP	19990325
				EP 1999-203478 A	19991022
				US 1999-449974 A	19991126
				WO 2000-NL171 W	20000313

OS CASREACT 133:252434; MARPAT 133:252434

GI



I

AB Imidazopyridines I (Y, Z = lower alkyl) were prepd. by reaction of 6-alkyl-2-(p-alkylphenyl)imidazo[1,2-a]pyridines with glyoxylic acid or its acetal. Thus, 22 g of 6-methyl-2-p-tolylimidazo[1,2-a]pyridine was suspended in 100 mL of dichloroethene, 10 g of glyoxylic acid monohydrate was added, and the mixt. was heated to reflux for 1.5 h to give 28 g of I (Y = Z = Me) with a purity of 97.9%.

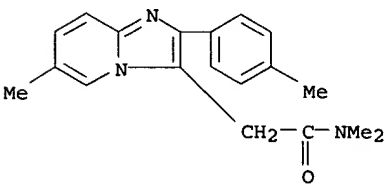
IT **99294-93-6P**, Zolpidem hemitartrate
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

RN 99294-93-6 CAPLUS

CN Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

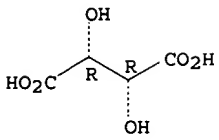
CRN 82626-48-0
CMF C19 H21 N3 O



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

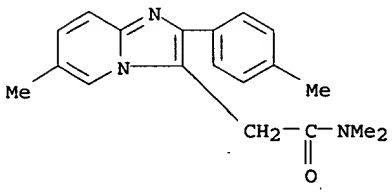
Absolute stereochemistry.



L6 ANSWER 9 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 2000:606269 CAPLUS
DN 134:153
TI Pharmacokinetics and relative bioavailability of zolpidem tartrate from tablets
AU Song, Hong-Jie; Li, Zhen; Shi, Jing; Fan, Guo-Rong; Jin, Gui-Lan; Hu, Jin-Hong
CS Department of Clinical Pharmacology, Shanghai Changhai Hospital, Shanghai, 200433, Peop. Rep. China
SO Zhongguo Linchuang Yaolixue Zazhi (2000), 16(2), 122-124
CODEN: ZLYZE9; ISSN: 1001-6821
PB Beijing Yike Daxue, Linchuang Yaoli Yanjiuso
DT Journal
LA Chinese
AB A single 10-mg oral dose of zolpidem tartrate in Chinese-manufd. (domestic) and imported (ref.) tablets were given to healthy volunteers in a randomized crossover study. HPLC with fluorimetric detection was used for detg. plasma zolpidem concns. A 1-compartment open model was fitted to the concn.- time curve. The pharmacokinetic parameters of the domestic and imported prepns. were, resp.: Cmax 121.36 and 124.40 .mu.g/L; Tmax 1.52 and 1.40 h; AUC0 495.62 and 467.29 .mu.g/h/L. The differences were nonsignificant. The two prepns. were bioequivalent. The relative bioavailability of the domestic tablets relative to the ref. prepn. was 103.59%.
IT **99294-93-6**, Zolpidem tartrate
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(pharmacokinetics and relative bioavailability in humans of zolpidem tartrate from tablets)
RN 99294-93-6 CAPLUS
CN Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

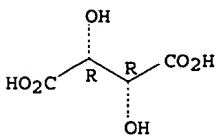
CRN 82626-48-0
CMF C19 H21 N3 O



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.



L6 ANSWER 10 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 2000:456854 CAPLUS

09/841025

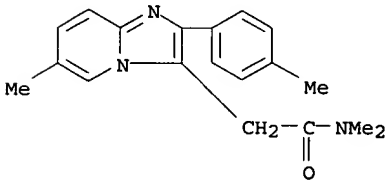
DN 133:79354
TI Pharmaceutical composition for oral administration designed to prevent misuse at the expense of a third party
IN Dufour, Alain; Ahond, Christian
PA Sanofi-Synthelabo, Fr.
SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000038649	A1	20000706	WO 1999-FR3120	19991214
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM ,				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
				FR 1998-16309 A	19981223
	FR 2787715	A1	20000630	FR 1998-16309	19981223
	EP 1140011	A1	20011010	EP 1999-959478	19991214
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
				FR 1998-16309 A	19981223
				WO 1999-FR3120 W	19991214

AB The invention concerns a pharmaceutical compn. for oral administration to prevent misuse at the expense of a third party. A three-layer 260 mg oral tablet contg. 15 mg zolpidem hemitartarate (I) in the active layer was prepd. The dissoln. of I was .gtoreq.80% after 15 min.
IT **99294-93-6**, Zolpidem hemitartrate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compn. for oral administration designed to prevent misuse at expense of third party)
RN 99294-93-6 CAPLUS
CN Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

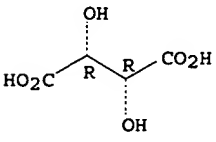
CRN 82626-48-0
CMF C19 H21 N3 O



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.



RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 11 OF 23 CAPLUS COPYRIGHT 2002 ACS

09/841025

AN 2000:383610 CAPLUS
DN 133:22433
TI Controlled-release dosage forms comprising a short acting hypnotic or a salt
IN Alaux, Gerard; Lewis, Gareth; Andre, Frederic
PA Synthelabo S. A., Fr.
SO Eur. Pat. Appl., 24 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 1005863	A1	20000607	EP 1998-403037	19981204
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	WO 2000033835	A1	20000615	WO 1999-EP10454	19991201
	W: AE, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
				EP 1998-403037 A	19981204
	BR 9915939	A	20010911	BR 1999-15939	19991201
				EP 1998-403037 A	19981204
				WO 1999-EP10454W	19991201
	EP 1135125	A1	20010926	EP 1999-968394	19991201
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
				EP 1998-403037 A	19981204
				WO 1999-EP10454W	19991201
	NO 2001002668	A	20010806	NO 2001-2668	20010530
				EP 1998-403037 A	19981204
				WO 1999-EP10454W	19991201

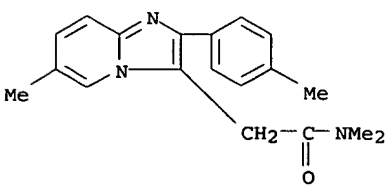
AB The present invention relates to controlled-release dosage forms of short acting hypnotics or salts thereof adapted to release the short acting hypnotic over a predetd. time period, according to a biphasic profile of dissoln., where the first phase is an immediate release phase and the second phase is a prolonged release phase. Thus, prolonged-release tablets comprising 10 mg zolpidem hemitartrate were prepd. from zolpidem hemitartrate 8.3, lactose 86.6, citric acid 2.5, HPMC-606 2.1, and Mg stearate 0.5%. Tablets were coated, in a pan coater, with a sufficient quantity of the following mixt. to obtain the desired dissoln. profile: Et cellulose 2.0, di-Et phthalate 0.4, HPMC-606 2.0, isopropanol 47.8, and dichloromethane 47.8%.

IT **99294-93-6**, Zolpidem hemitartrate
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(controlled-release dosage forms comprising hypnotic or a salt)

RN 99294-93-6 CAPLUS
CN Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

CRN 82626-48-0
CMF C19 H21 N3 O



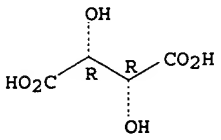
CM 2

CRN 87-69-4
CMF C4 H6 O6

09/841025

CDES 1:R2:R*,R*

Absolute stereochemistry.



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

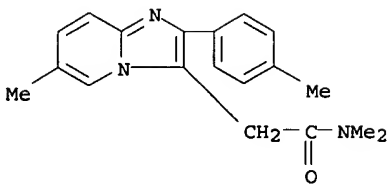
L6 ANSWER 12 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 2000:117049 CAPLUS
DN 132:151822
TI Process for preparing N,N,6-trimethyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acetamide and salts thereof
IN Labriola, Rafael
PA Quimica Sintetica, S.A., Spain
SO PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DT Patent
LA Spanish
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000008021	A2	20000217	WO 1999-ES250	19990804
WO 2000008021	A3	20000706		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
			ES 1998-1694 A	19980806
ES 2151834	A1	20010101	ES 1998-1694	19980806
ES 2151834	B1	20010816		
AU 9952912	A1	20000228	AU 1999-52912	19990804
			ES 1998-1694 A	19980806
			WO 1999-ES250 W	19990804
EP 1104765	A2	20010606	EP 1999-938403	19990804
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
			ES 1998-1694 A	19980806
			WO 1999-ES250 W	19990804
NO 2001000613	A	20010205	NO 2001-613	20010205
			ES 1998-1694 A	19980806
			WO 1999-ES250 W	19990804

OS CASREACT 132:151822
AB The title compd. was prepd. by treating 2-amino-5-methylpyridine with 4-MeC6H4COCH2Br to give 6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine which was treated with HCOCH2CO2Me to give the 3-(.alpha.-hydroxyacetate). The latter compd. was dehydroxylated by treatment with ClCH:N+Me2 Cl- and redn. and amidated to give the title compd.
IT **99294-93-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of N,N,6-trimethyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acetamide and salts thereof)
RN 99294-93-6 CAPLUS
CN Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

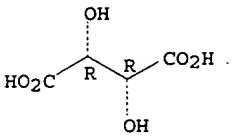
CRN 82626-48-0
CMF C19 H21 N3 O



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

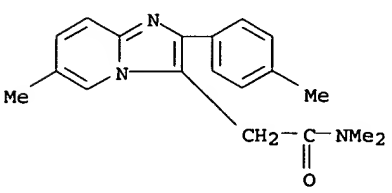
Absolute stereochemistry.



L6 ANSWER 13 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 1999:25458 CAPLUS
DN 130:261922
TI Continuous flumazenil infusion in the treatment of zolpidem (Ambien) and ethanol coingestion
AU Burton, John H.; Lyon, Lawrence; Dorfman, Todd; Tomassoni, Anthony J.
CS Maine Medical Center, Portland, ME, USA
SO J. Toxicol., Clin. Toxicol. (1998), 36(7), 743-744
CODEN: JTCTDW; ISSN: 0731-3810
PB Marcel Dekker, Inc.
DT Journal
LA English
AB Zolpidem tartrate (Ambien) is an imidazopyridine sedative with a high affinity with the supramol. complex that includes the .gamma.-aminobutyric acid (GABA) benzodiazepine receptors and the chloride channel. Overdose with zolpidem does not typically require therapeutic interventions. However acute zolpidem co-ingestion with other drugs specifically alc. can result in profound central nervous system (CNS) depression. Response to administration of flumazenil has been reported in zolpidem overdose. A case of a woman with profound CNS depression resulting from coingestion of alc. and zolpidem successfully treated with an 8-h flumazenil infusion.
IT **99294-93-6**, Ambien
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(continuous flumazenil infusion in treatment of central nervous system depression from combined zolpidem and ethanol ingestion)
RN 99294-93-6 CAPLUS
CN Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

CRN 82626-48-0
CMF C19 H21 N3 O



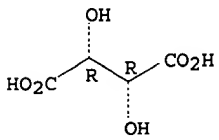
CM 2

CRN 87-69-4

09/841025

CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.

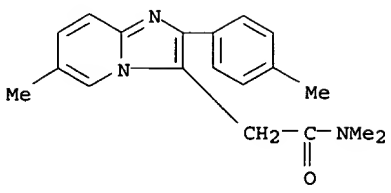


RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 14 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 1997:70207 CAPLUS
DN 126:166371
TI Discriminative stimulus effects of zolpidem in pentobarbital-trained subjects: I. Comparison with triazolam in rhesus monkeys and rats
AU Rowlett, James K.; Woolverton, William L.
CS Dep. Psychiatry, Univ. Mississippi Med. Cent., Jackson, MS, USA
SO J. Pharmacol. Exp. Ther. (1997), 280(1), 162-173
CODEN: JPETAB; ISSN: 0022-3565
PB Williams & Wilkins
DT Journal
LA English
AB The present study compared the discriminative stimulus effects of the imidazopyridine, zolpidem, with a triazolobenzodiazepine, triazolam, in pentobarbital-trained rhesus monkeys and rats. Rhesus monkeys, trained to discriminate pentobarbital (10 mg/kg intragastric [i.g/]) from saline under a FR 1 discrete-trials shock avoidance procedure, were given zolpidem (0.10-30 mg/kg, i.g.) or triazolam (0.01-0.3 mg/kg i.g.). Both zolpidem and triazolam produced dose-dependent increases in pentobarbital-appropriate responding that reached 80% or greater at the highest doses tested. Zolpidem, but not triazolam, increased latency to respond in a dose-dependent manner. Sprague-Dawley rats, trained to discriminate pentobarbital (8.0 mg/kg i.p.) from saline under a FR 10 schedule of food reinforcement, were given zolpidem (0.50-4.0 mg/kg i.p.; 5-, 15- and 45-min pretreatment) or triazolam (0.025-0.20 mg/kg i.p., 15-min pretreatment). Zolpidem occasioned intermediate drug-appropriate responding (max. group mean = 46%) at the 5- and 15-m in pretreatment times and no drug-appropriate responding at the 45-min pretreatment time. In contrast, triazolam occasioned .gtoreq.80% pentobarbital-appropriate responding at 0.10 and 0.20 mg/kg. Both zolpidem and triazolam produced dose-dependent decreases in the rate of responding. The rate-decreasing effects of zolpidem were maximal at the 5-min pretreatment time and had dissipated after the 45-min pretreatment time. Further studies were conducted in rats to equate procedural variables between the monkey and rat studies. When the FR was reduced from 10 to 1, zolpidem occasioned 26 to 62% pentobarbital-appropriate responding over a dose range of 1.0 to 6.0 mg/kg i.p. After i.g. administration at the highest dose tested (6.0 mg/kg); however, only two of seven rats responded. Taken together, these data raise the possibility of a species difference between nonhuman primates and rats in the pentobarbital-like discriminative stimulus effects of zolpidem.
IT **99294-93-6**, Zolpidem tartrate
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(discriminative stimulus effects of zolpidem in pentobarbital-trained subjects and comparison with triazolam in rhesus monkeys and rats)
RN 99294-93-6 CAPLUS
CN Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

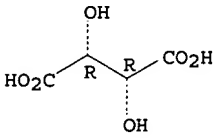
CRN 82626-48-0
CMF C19 H21 N3 O



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.



L6 ANSWER 15 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 1995:856174 CAPLUS
DN 123:246794
TI Method for preventing or reducing photosensitivity and/or phototoxicity reactions to medications
IN Klimstra, Paul Dale; Roniker, Barbara; Swabb, Edward Allen
PA G. D. Searle and Co., USA
SO PCT Int. Appl., 137 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9520387	A1	19950803	WO 1995-US213	19950112
	W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US				
	RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
				US 1994-188296 A119940128	
	US 5668134	A	19970916	US 1994-188296	19940128
	AU 9515605	A1	19950815	AU 1995-15605	19950112
				US 1994-188296 A	19940128
				WO 1995-US213 W	19950112
	EP 741570	A1	19961113	EP 1995-907337	19950112
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
				US 1994-188296 A	19940128
				WO 1995-US213 W	19950112
	US 6172069	B1	20010109	US 1997-936572	19970924
				US 1994-188296 A1	19940128
				US 1995-438002 B1	19950509

AB A method for preventing or reducing a photosensitivity and/or phototoxicity reaction which may be caused by a once-per-day dose of a medication comprises administering the prescribed or suggested dose of the medication to the patient during the evening or early morning hours. The present invention also provides a method for treating an infection in a patient in a manner which prevents or reduces a photosensitivity and/or phototoxicity reaction which method comprises orally administering to the patient a once-a-day dose of 25-700 mg of lomefloxacin HCl during the evening or early morning hours. The present invention also provides an article of manuf. comprising: (1) a packaging material, and (2) a once-a-day medication which causes a photosensitivity and/or a phototoxicity reaction in a patient contained within said packaging material and wherein said packaging material comprises a label which indicates that such a reaction is prevented or reduced by administering the medication to the patient during the evening or early morning hours.
IT **99294-93-6**, Zolpidem tartrate

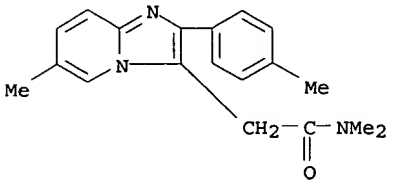
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for preventing or reducing photosensitivity and/or phototoxicity reactions to drugs in humans)

RN 99294-93-6 CAPLUS

CN Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

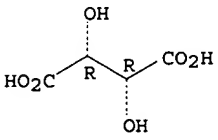
CRN 82626-48-0
CMF C19 H21 N3 O



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.



L6 ANSWER 16 OF 23 CAPLUS COPYRIGHT 2002 ACS

AN 1994:68794 CAPLUS

DN 120:68794

TI Metabolic fate of zolpidem. (IV). Serum and plasma protein binding of zolpidem and its transfer into the blood cells in rats, monkeys and humans

AU Ishibashi, Koji; Hashimoto, Tomoko; Katashima, Masataka; Tokuma, Yoji; Noda, Kosei

CS Prod. Dev. Lab., Fujisawa Pharm. Co., Ltd., Osaka, 532, Japan

SO Yakubutsu Dotai (1993), 8(4), 445-55
CODEN: YADOEL; ISSN: 0916-1139

DT Journal

LA Japanese

AB In vitro and in vivo protein binding of zolpidem and its transfer into the blood cells were studied in rats, monkeys and humans. The results are summarized as follows. In a range of 50 to 5000 ng/mL, the in vitro percent binding of zolpidem to serum proteins in rats, monkeys and humans was 86.6-86.9, 92.4-93.9 and 94.5-96.0%, resp. Zolpidem was bound to two classes of sites with different affinities of human serum albumin and .alpha.1-acid glycoprotein (AGP). The assocn. consts. (Ka, M-1) and binding capacities (NP, M) of zolpidem to these proteins were as follows. Albumin: Ka1 = 1.8 .times. 105, N1P = 2.9 .times. 10-6, Ka2 = 4.2 .times. 103, N2P = 2.1 .times. 10-4 .alpha.1-AGP: Ka1 = 6.0 .times. 105, N1P = 6.3 .times. 10-6, Ka2 = 2.0 .times. 104, N2P = 2.5 .times. 10-5. The percent binding of zolpidem in 40 mg/mL human albumin soln. was 83.4-85.5% and was almost const. over a range of 50-5000 ng/mL. Zolpidem also was highly bound to human .alpha.1-AGP (1 mg/mL) but the percent binding of the drug decreased from 83.1% at 50 ng/mL to 55.5% at 5000 ng/mL. On the other hand, the percent binding of zolpidem in 16 mg/mL human globulin soln. was 19.5-21.6%, lower than those in human albumin and .alpha.1-AGP solns. Consequently, albumin and .alpha.1-AGP would be responsible for the binding of zolpidem to human serum proteins. The in vivo percent binding of zolpidem was 83.2-83.8% in rat plasma and 96.0-96.3% in human plasma. These bound fractions were almost the same as the in vitro bound fractions measured simultaneously, indicating that the in vivo plasma protein binding of zolpidem in rats and humans would not be affected significantly by its metabolites. The transfer rates of zolpidem into the blood cells

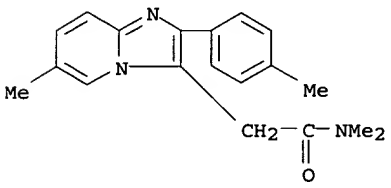
were 31.6-36.1% for rats, 30.8-36.6% for monkeys and 17.5 .apprx. 18.5% for humans, and no a significant correlation between the free fractions in the plasma and the transfer rates into the blood cells was obsd.

IT **99294-93-6**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metab. of, plasma protein binding and transport to blood cells in, species difference in)

RN 99294-93-6 CAPLUS
CN Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

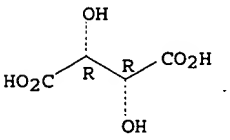
CRN 82626-48-0
CMF C19 H21 N3 O



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.

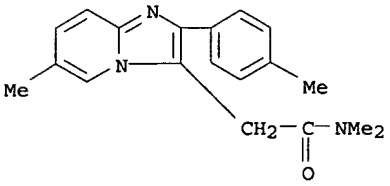


L6 ANSWER 17 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 1994:68793 CAPLUS
DN 120:68793
TI Metabolic fate of zolpidem. (III). Transfer into the fetus and milk in rats after single oral dosing
AU Ishibashi, Koji; Tokuma, Yoji; Noda, Kaosei; Esumi, Yoshio; Katami, Yoshiharu; Sugai, Saburo
CS Prod. Dev. Lab., Fujisawa Pharm. Co., Ltd., Osaka, 532, Japan
SO Yakubutsu Dotai (1993), 8(4), 437-44
CODEN: YADOEL; ISSN: 0916-1139
DT Journal
LA Japanese
AB 14C-zolpidem hemitartrate, a new hypnotic drug, was given orally in a dose of 3.29 mg/kg to pregnant and lactating rats and its transfer into the fetus and milk was studied. The results are summarized as follows. After oral dosing to a rat on day 18 of gestation, the radioactivity in the fetus was lower than that in the maternal blood. The radioactivity in the fetal tissues declined rapidly, and no radioactivity was detected 48 h after dosing. The whole body autoradiograms of rats, which were given the 14C-labeled compd. orally on days 13 and 18 of gestation, showed that the radioactivity in the fetus was lower than that in the maternal blood and that distribution of radioactivity to the fetus was higher in the perinatal period than in the organogenic period. Thirty minutes after oral dosing to lactating rats, the radioactivity in the milk reached a max. of 267 ng eq/mL, and then declined with a half-life of 4.9 h up to 24 h. The radioactivity levels in the milk were almost the same or lower than those in the plasma up to 4 h after dosing, but were 1.1-1.8 times higher thereafter. The ratio of AUCm to AUCp, which was calcd. from the concns. of radioactivity in milk and plasma resp., was about 0.65. This suggested that zolpidem and/or its metabolites were less easily transferred into the milk.
IT **99294-93-6**, Zolpidem tartrate
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)

(metab. of, transfer into fetus and milk in relation to)
RN 99294-93-6 CAPLUS
CN Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

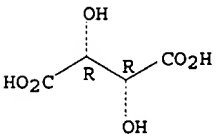
CRN 82626-48-0
CMF C19 H21 N3 O



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.

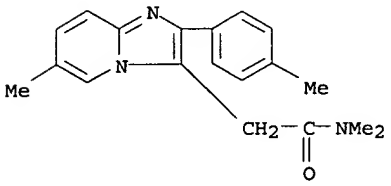


L6 ANSWER 18 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 1994:68792 CAPLUS
DN 120:68792
TI Metabolic fate of zolpidem. (II). Pharmacokinetics of zolpidem in rats after multiple oral dosing
AU Ishibashi, Koji; Tokuma, Yoji; Noda, Kosei; Esumi, Yoshio; Katami, Yoshiharu; Ninomiya, Shinichi
CS Prod. Dev. Lab., Fujisawa Pharm. Co., Ltd., Osaka, 532, Japan
SO Yakubutsu Dotai (1993), 8(4), 427-35
CODEN: YADOEL; ISSN: 0916-1139
DT Journal
LA Japanese
AB The 14C-labeled compd. of zolpidem hemitartrate, a new hypnotic drug, was given orally in a dose of 3.29 mg/kg to male rats once a day for a max. of 28 days, and its absorption, distribution, metab. and excretion were examd. The results are summarized as follows. Area under the blood radioactivity-time curves (AUCs) up to 24 h after the 1st, 7th, 14th, 21st and 28th dosing were 1.74, 1.35, 1.92, 1.73 and 2.14 .mu.g eq. hr/mL resp. Since there was no the difference among AUCs after the 14th, 21st and 28th dosing, the blood radioactivity was considered to have reached a steady state. The increase of AUCs during multiple dosing was of low extent because those after the 14th and 28th dosing were only 1.1 and 1.2 times higher than those after the 1st dosing. Tissue to plasma concn. ratios of radioactivity after the 14th or 21st dosing were almost const. in many tissues including the blood, lung, liver, kidneys and skin whose the concns. of radioactivity were higher than in the plasma. This showed that the tissue radioactivity was probably reaching a steady state after the 14th or 21st dosing. The disappearance of radioactivity after the 28th dosing was slower in the kidneys, spleen and skin than that in the plasma. Seventy two hours after the last dosing, however, the concns. of radioactivity in these tissues were less tan 1% of the 5 min-value, and no radioactivity was detected at 70 days. After the 28th dosing, the zolpidem was not detected in the urine and feces, and metabolites accounted for radioactivity excreted in the urine and feces, resp. The metab. of zolpidem was unaffected by multiple oral dosing (28 times). Urinary and fecal excretion of radioactivity was almost const. during multiple oral dosing.
IT **99294-93-6**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)

(pharmacokinetics of, after multiple dosing)
RN 99294-93-6 CAPLUS
CN Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

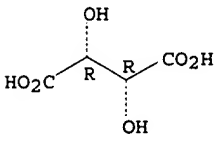
CRN 82626-48-0
CMF C19 H21 N3 O



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.

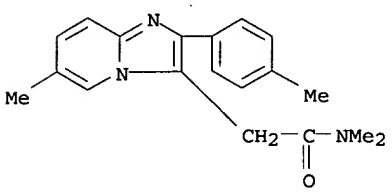


L6 ANSWER 19 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 1994:68791 CAPLUS
DN 120:68791
TI Metabolic fate of zolpidem. (I). Pharmacokinetics of zolpidem in rats after single dosing
AU Ishibashi, Koji; Hashimoto, Tomoko; Tokuma, Yoji; Noda, Kosei; Esumi, Yoshio; Katami, Yoshiharu; Ninomiya, Shinichi
CS Fujisawa Pharm. Co., Ltd., Osaka, 532, Japan
SO Yakubutsu Dotai (1993), 8(4), 413-25
CODEN: YADOEL; ISSN: 0916-1139
DT Journal
LA Japanese
AB 14C-labeled or non-labeled zolpidem hemitartrate, a new hypnotic drug, was given i.v., intraportally or orally to male rats and its pharmacokinetics was examd. The results are summarized as follows. After i.v. dosing of 3.29 mg/kg of zolpidem hemitartrate, the zolpidem in the plasma disappeared biexponentially with a terminal elimination half-life of 1.11 h. After oral dosing of 0.66, 3.29 or 16.45 mg/kg, zolpidem was absorbed rapidly from the gastrointestinal tract with Tmax of 5 min. Linear relationships between AUC, Cmax and the dose were obsd., indicating that the pharmacokinetics of zolpidem after oral dosing is linear. The bioavailabilities of zolpidem after oral and intraportal dosing were 45.8 and 46.2%, resp., suggesting that the oral absorption of 14C-zolpidem was almost complete and that about 54% of oral dose might undergo first-pass metab. in the liver. Thirty minutes after oral dosing of 3.29 mg/kg of 14C-zolpidem hemitartrate, the tissue concns. of radioactivity in the liver, kidneys, adrenal gland, brown fat, urinary bladder, stomach and small intestine were higher than those in the plasma. Twenty-four hours after dosing, the concns. of radioactivity in the liver, kidneys, skin and large intestine were 13.apprx.42 ng eq/g, but no radioactivity was detected in the other tissues. A carboxylic acid deriv. of zolpidem was the main metabolite in the plasma, urine, feces and bile of rats. This shows that the main metabolic pathway of zolpidem in rats is Me oxidn. on the Ph moiety leading to alc. and carboxylic acid derivs. Radioactivity (23.7% of the dose) was excreted in the urine and 74.2% in the feces up to 120 h after oral dosing. Sixty seven % of the dosed radioactivity was excreted in the bile of bile-duct cannulated rats up to 48 h after oral dosing. Thus, the principal excretion route of radioactivity in rats was the feces via the bile.

IT **99294-93-6**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(pharmacokinetics of)
RN 99294-93-6 CAPLUS
CN Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

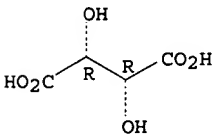
CRN 82626-48-0
CMF C19 H21 N3 O



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

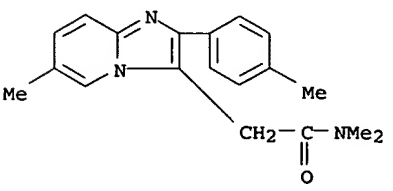
Absolute stereochemistry.



L6 ANSWER 20 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 1992:228040 CAPLUS
DN 116:228040
TI On the effects of zolpidem to nocturnal sleep. A whole night polysomnographic study in normal subjects
AU Nobuhara, Kenji; Isotani, Toshiaki; Okajima, Yoshiyasu; Saito, Akemi; Yagyu, Takami; Saito, Naomi; Nishimura, Takahiro; Ohashi, Yoshiki; Kitashiro, Mami; et al.
CS Dep. Neuropsychiatry, Kansai Med. Univ., Moriguchi, 570, Japan
SO Shinkei Seishin Yakuri (1992), 14(2), 137-44
CODEN: SSYAD7; ISSN: 0388-7588
DT Journal
LA Japanese
AB Zolpidem tartrate (10 mg) showed hypnotic effect without affecting the rhythm and quality of nocturnal sleep in healthy male adults.
IT **99294-93-6**, Zolpidem tartrate
RL: BIOL (Biological study)
(sleep response to, in humans)
RN 99294-93-6 CAPLUS
CN Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

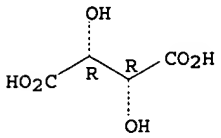
CRN 82626-48-0
CMF C19 H21 N3 O



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.



L6 ANSWER 21 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 1989:23888 CAPLUS
DN 110:23888
TI Process for the preparation of (2-phenylimidazopyridinyl)acetamides
IN Rossey, Guy; Long, David
PA Synthelabo S. A., Fr.
SO Fr. Demande, 11 pp.
CODEN: FRXXBL
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	FR 2600650	A1	19871231	FR 1986-9330	19860627
	FR 2600650	B1	19880909		
	EP 251859	A2	19880107	EP 1987-401353	19870617
	EP 251859	A3	19890719		
	EP 251859	B1	19901122		
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
				FR 1986-9330	19860627
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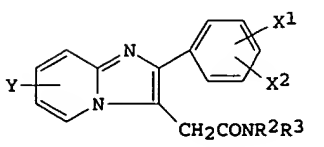
GI



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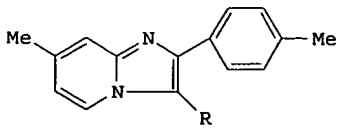


III

09/841025

AB The title compds. (I; R2, R3 = H, C1-5 alkyl; X1, X2 = H, halo, C1-4 alkoxy, C1-6 alkyl, CF3, MeS, MeSO2, NO2; Y = H, halo, C1-4 alkyl) were prepd. by condensation of a phenylimidazopyridine with R2R3NCOCH(OR4)2 (R4 = C1-4 alkyl) (II) followed by chlorination and hydrogenolysis. Thus, II were hydrolized to the carbamoylaldehyde which was refluxed with phenylimidazopyridine III (R = H) to give III (R = CH(OH)CONMe2) which was refluxed with SOCl2 1 h in (ClCH2)2 to give III (R = CHClCONMe2). The latter was stirred 1.5 h with NaS2O4 in aq. MeOH contg. HCHO to give 81.6% III (R = CH2CONMe2).

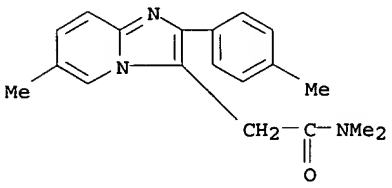
IT **99294-93-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

RN 99294-93-6 CAPLUS

CN Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

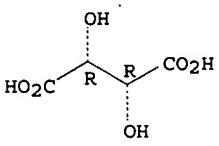
CRN 82626-48-0
CMF C19 H21 N3 O



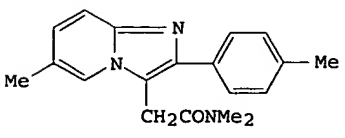
CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.



L6 ANSWER 22 OF 23 CAPLUS COPYRIGHT 2002 ACS
AN 1988:160846 CAPLUS
DN 108:160846
TI Thermospray liquid chromatography tandem mass spectrometry: application to the elucidation of zolpidem metabolism
AU Vajta, S.; Thenot, J. P.; De Maack, F.; Devant, G.; Lesieur, M.
CS Lab. Etud. Rech. Synthelabo, Paris, 75013, Fr.
SO Biomed. Environ. Mass Spectrom. (1988), 15(4), 223-8
CODEN: BEMSEN; ISSN: 0887-6134
DT Journal
LA English
GI



I

AB Zolpidem (I) metabolites were identified in rat urine by thermospray liq. chromatog./tandem mass spectrometry LC/MS/MS. When compared to other chromatog./mass spectrometric-based techniques, reversed phase HPLC

coupled with thermospray LC/MS/MS appears to be the fastest method available today for elucidation of unknown metabolic structures, since it allows identification by direct injection of concd. urine. However, it was noted during the thermospray process that loss of formaldehyde from a hydroxymethyl amide metabolite occurred. This degrdn. was not obsd. when this metabolite was analyzed by gas chromatog./mass spectrometry following trimethylsilylation.

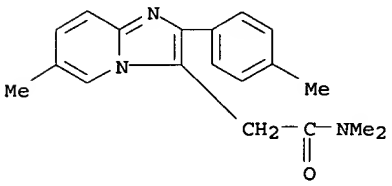
IT **99294-93-6**, Zolpidem tartrate
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metab. of, urinary metabolites identification by thermospray liq. chromatog. with tandem mass spectrometry in)

RN 99294-93-6 CAPLUS

CN Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

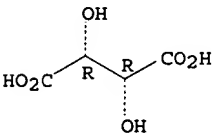
CRN 82626-48-0
CMF C19 H21 N3 O



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.



L6 ANSWER 23 OF 23 CAPLUS COPYRIGHT 2002 ACS

AN 1987:43333 CAPLUS

DN 106:43333

TI High-performance liquid chromatographic determination of zolpidem, a new sleep inducer, in biological fluids with fluorimetric detection

AU Guinebault, P.; Dubruc, C.; Hermann, P.; Thenot, J. P.

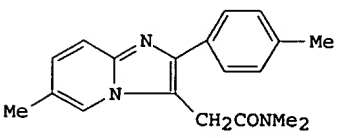
CS Lab. Etud. Rech. Synthelabo, Meudon la Foret, 92360, Fr.

SO J. Chromatogr. (1986), 383(1), 206-11
CODEN: JOCRAM; ISSN: 0021-9673

DT Journal

LA English

GI



I

AB Zolpidem (I) [82626-48-0] and the internal std. N,6-dimethyl-2-(4-methylphenyl)-N-propylimidazo[1,2-a]pyridine-3-acetamide were extd. from alkalinized blood or plasma with Et2O. HPLC of the compds. was performed on a Spherisorb ODS-2 5-.mu.m column; the mobile phase consisted of

MeCN-KH2PO4 (70:30). Fluorescence detection was performed with excitation and emission wavelengths of 254 and 390 nm, resp. Calibration curves were linear 1-400 ng/mL blood and the lower limit of detection was 0.5 ng/mL. The reproducibility of the method was checked for 3 blood concns. (10, 50, and 150 ng/mL) and the coeffs. of variation were 7.2, 9.5, and 6.3%, resp. I in blood samples at 10 ng/mL was stable up to 24 h at 37.degree.. This method was used to det. plasma concns. of I following administration of a single 20 mg oral or a single 8 mg i.v. dose of I hemitartrate [**99294-93-6**] to a healthy subject. Blood levels peaked at .apprx.200 ng/mL 30 min after oral administration and decayed with a half-life of .apprx.2 h.

IT **99294-93-6**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(pharmacokinetics of, in humans)

RN 99294-93-6 CAPLUS
CN Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)

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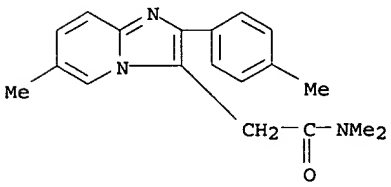
CRN 82626-48-0
CMF C19 H21 N3 O



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.